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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
RAWLINGS, STEPHEN L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/357,704	BANDER, NEIL H.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-80,124-127,129,130,136-173,186 and 190* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-80, 124-127, 129, 130, 136-173, 186, and 190* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20060822* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the rejection of the last Office action mailed July 9, 2004, is withdrawn; and prosecution on the merits of this application is reopened on claims 69-80, 124-127, 129, 130, 136-173, 186, and 190, which are considered unpatentable for the reasons indicated below.

2. Claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 are pending in the application and are currently subject to examination.

Grounds of Objection and Rejection Withdrawn

3: The grounds of rejection set forth in the previous Office action mailed July 9, 2004, have been withdrawn.

Response to Arguments

4. Applicant's arguments with respect to claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 have been considered but are moot in view of the new ground(s) of rejection.

Priority

5. Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the U.S. Patent Application No. 08/838,682, filed April 9, 1997, which claims benefit of U.S. Provisional Application No. 60/022,125, filed July 18, 1996, and U.S. Provisional Application No. 60/016,976, filed May 6, 1996, is acknowledged.

However, claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 is deemed the filing date of the instant application, namely July 20, 1999.

New Grounds of Objection

Specification

6. The specification is objected to for the following reason:

At page 1, paragraph 1, of the specification there is a statement that this application is a division of Application Serial No. 08/836,682. The prior filed application has since issued as U.S. Patent No. 6,107,090; yet the specification does not properly indicate the status of this application. Appropriate correction is required.

Claims

7. Claims 79 80, 172, and 173 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 79 is drawn in the alternative to an invention selected from the following:

(a) The method of claim 78, wherein the antibody is an E99 monoclonal antibody;

(b) The method of claim 78, wherein the antibody is a J533 monoclonal antibody;

(c) The method of claim 78, wherein the antibody is a J415 monoclonal antibody; and

(d) The method of claim 78, wherein the antibody is a J591 monoclonal antibody.

Claim 78 is drawn to the method of claim 69, wherein the antibody is a monoclonal antibody or a polyclonal antibody; and claim 69 is drawn to a method of treating prostate cancer comprising providing and administering to a subject an antibody or antigen binding portion that competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody.

The specification describes an E99, a J533, and a J591 monoclonal antibody, which bind to competing binding sites (i.e., they compete with one another for binding to PSMA); see, e.g., page 38, lines 11-16. The only monoclonal antibody that is described in the specification, which binds to a non-competing binding site, as compared to the monoclonal antibodies E99, J533, and J591, as it does not compete for binding to PSMA with these other monoclonal antibodies, is monoclonal antibody J415.

Therefore, insofar as claim 79 is drawn to the method of claim 78, wherein the antibody is any one of an E99, a J533, and a J591 monoclonal antibody, it is aptly noted that claim 79 properly limits the preceding claims; however, insofar as claim 79 is drawn to the method of claim 78, wherein the antibody is a J415 monoclonal antibody, it fails to properly limit the subject matter of the preceding claims because, although the limitations recited in claim 69 require the antibody to compete for binding to PSMA with any a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, the specification describes the J415 monoclonal antibody as incapable of competing with an E99, a J533, or a J591 monoclonal antibody.

To properly limit the subject matter of a preceding claim, a dependent claim must limit each embodiment of the preceding claim, or must be written in a manner that makes evident that it is directed to only those embodiments of the preceding claim, which are further limited by its recitation.

Claim 80 fails to properly further limit the subject matter of claim 78 for essentially the same reason, as it is drawn in the alternative to the method of claim 78, wherein the

antibody is a monoclonal antibody produced by a hybridoma having an ATCC accession number selected from the group consisting of HB-12101, HB-12109, HB-12127, and HB-12126, which are described as producing monoclonal antibodies E99, J415, J533, and J591, respectively; see, e.g., page 30, lines 21-27.

Claim 172 fails to properly further limit the subject matter of claim 126 for the reason claim 79 fails to properly further limit the subject matter of claim 78, which is provided in the paragraph above; and claim 173 fails to properly further limit the subject matter of claim 126 for the reason claim 80 fails to properly further limit the subject matter of claim 78.

Appropriate correction is required.

8. Claim 136 is objected to because it recites, "wherein the antibody is a monoclonal antibody or the antigen binding portion thereof is derived from a monoclonal antibody". A monoclonal antibody is a monoclonal antibody; so, how is the monoclonal antibody to which the claim is directed *derived from a monoclonal antibody*? Furthermore, if the antigen binding portion is an antigen binding portion of the antibody, which is a monoclonal antibody, is the portion to which the claim is directed not necessarily *derived from a monoclonal antibody*? Under 37 CFR 1.75(c), a dependent claim form must further limit the subject matter of the previous claims. It is not clear if, and then how claim 136 is intended to further limit the preceding claim.

Appropriate rebuttal or correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 are directed to a genus of antibodies or antigen-binding fragments thereof, which compete for binding to PSMA with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533 and a J591 monoclonal antibody.

The claims are indefinite for the following reasons:

(a) The claims are indefinite because of the recitation in claim 69, for example, of "a monoclonal antibody selected from the group consisting of *an* E99, *a* J415, *a* J533 and *a* J591 monoclonal antibody" (italics added for emphasis). Although the specification describes deposited hybridomas that produce monoclonal antibodies designated "E99" (deposit accession number ATCC HB-12101), "J415" (deposit accession number ATCC HB-12109), "J533" (deposit accession number ATCC HB-12127), and "J591" (deposit accession number ATCC HB-12126)[1], the claims appear directed to one or another genus of a *plurality* of monoclonal antibodies, which are designated "E99", "J415", "J533", or "J591", and which are not necessarily the monoclonal antibodies produced by any of the deposited hybridomas. Use of such laboratory designations as the sole means of identifying the antibodies to which the claims are directed renders the claims indefinite because different laboratories may use the same designations to define completely distinct hybridomas and/or the antibodies produced by hybridomas.

Therefore, because the use of such designations as descriptors of the antibodies renders the claims subject to ambiguous interpretation, the metes and bounds of the subject matter that is regarded as the invention cannot be determined the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Accordingly, it is suggested that the claims be amended to include the depository accession numbers of the hybridomas producing the antibodies to which the claims are directed because a depository accession number uniquely identifies a deposited

[1] See the specification, e.g., at page 19, Table 1.

hybridoma, so as to unambiguously define the monoclonal antibody to which a claim is directed.

(b) The claims are indefinite because of the recitation in claim 69, for example, of "which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody" selected from the specified group of monoclonal antibodies.

At page 27, lines 33-35, for example, of the specification discloses: "Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays". The specification describes the binding assay, which was used to determine, allegedly, whether monoclonal antibodies J591, J533, E99, and J415 detect the same or different epitopes; see, e.g., page 37, line 23, through page 38, line 25. As explained at page 38, lines 5-10, the controls used as the basis for this determination consisted of using the same monoclonal antibody both cold and labeled to define "100% competition", or using monoclonal antibody to a totally different molecule (e.g., monoclonal antibody I-56, which detects inhibin) to define "0% competition". Thus, according to these disclosures, it is evident that one determines whether an antibody "competes" for binding to PSMA with one of the selected antibodies by measuring the percentage of binding of a detectably labeled antibody in the presence of an unlabeled (i.e., "cold") antibody.

Nevertheless, it is aptly noted that the term "competes" is not expressly defined in the specification, so it may not be immediately clear what functional attribute characterizes the claimed antibody or antigen binding fragment thereof; moreover, as discussed in greater detail below, the degree to which the claimed antibody "competes" for binding to PSMA with any one of the recited monoclonal antibodies, nor the methodology used to make the determination, and the conditions under which that determination are made, are not delineated by the claims and are not ascertainable from the disclosure.

The term "competition" is defined, for example, by Stedman's Online Medical Dictionary, 27th Edition as meaning: "The process by which the activity or presence of one substance interferes with, or suppresses, the activity of another substance with

similar affinities" (Copyright © 2006 Lippincott Williams & Wilkins). Given this definition, the claims are directed to antibodies or antigen-binding fragments thereof that interfere with, or suppress binding of one of the selected monoclonal antibodies to PSMA, as perhaps determined using the exemplified binding assay.

This interpretation is not inconsistent with the specification, which at page 38, lines 11-13, for example, discloses: "The results indicated that J591, J533, and E99 each **interfere, compete, or block** binding of one another but do not block binding of J415 and vice versa" (emboldened for emphasis).

Thus, while one may know how to determine whether an antibody "competes" with one of the selected monoclonal antibodies, it is apparent that the degree to which an antibody competes with another antibody is a relative or subjective expression, and the requisite degree to which the claimed antibody competes with any of the selected monoclonal antibodies cannot be ascertained from the disclosure.

Contrary to the assertion in the specification that such a binding assay determines whether two antibodies bind to the same antigenic determinant (i.e., epitope), competing antibodies do not necessarily bind the same epitopes. For example, "competing" antibodies may bind spatially overlapping but discrete epitopes. Simply because two antibodies cannot simultaneously occupy the same space, such an antibody, once bound to the antigen, sterically hinders or blocks binding of another such antibody. As another example, a "competing" antibody might not necessarily bind to the same epitope of an antigen as another antibody, if one of the antibodies induces conformational shifts in the three-dimensional structure of the antigen upon binding, which prevents binding of the other antibody to the antigen because the epitope to which it would otherwise bind is unrecognizable as a consequence of the structural change.

In addition, it is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any

antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

George et al. (*Circulation*. 1998; **97**: 900-906), for example, describes different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of competing with one another for binding to the antigen; see entire document (e.g., page 903, paragraph bridging columns 1 and 2). More particularly, George et al. describes three antibodies, which bind decidedly different, non-cross-reactive epitopes on β2GPI; yet, George et al. teaches each is able to "compete" *to some extent* with any of the others for binding to the antigen (page 903, paragraph bridging columns 1 and 2). For example, George et al. teaches monoclonal antibody ILA-4 competed with itself for binding to the antigen (% inhibition = 90 ± 11% at competitor antibody concentrations of 30 μg/ml), but George et al. discloses, despite its binding a non-overlapping epitope, monoclonal antibody ILA-1 also "competed", albeit perhaps unsubstantially with monoclonal antibody ILA-4 for binding to the antigen (% inhibition = 9 ± 4%).

Accordingly, George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification. Although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

Therefore, the claims are *not* unambiguously interpreted, as it cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the selected antibody and PSMA. Moreover, if the claimed antibody merely inhibits binding of the selected antibody to PSMA, it cannot be determined to what requisite extent the claimed antibody must "compete" for binding to PSMA with the selected antibody.

Finally, as explained above in subsection (a) of this rejection, the claims are not necessarily limited to the antibodies produced by any of the deposited hybridomas, as they are instead more broadly directed to antibodies that compete for binding to PSMA with any of a *plurality* of "E99" monoclonal antibodies, any of a *plurality* of "J415" monoclonal antibodies, any of a *plurality* of "J533" monoclonal antibodies, or any of a *plurality* of "J591" monoclonal antibodies. Pointedly, different members of these different pluralities of antibodies do not necessarily bind PSMA with the same affinity or avidity as any of the monoclonal antibodies produced by any of the deposited hybridomas. For example, a humanized "J591" antibody may have a substantially different binding affinity than the murine monoclonal antibody produced the deposited hybridoma. Presuming the concentration of the antibody is not altered, depending upon the affinity and avidity that characterizes any given antibody's ability to bind an antigen, the antibody is expected to more or less effectively "compete" with another antibody that binds the same antigen.

Consequently, the metes and bounds of the subject matter encompassed by the claims vary, depending upon one's interpretation of the language of those claims, as well as upon the binding characteristics of the antibody that is selected from any of the recited pluralities of monoclonal antibodies; and while notably claims could and should be given the broadest, reasonable interpretation, it is submitted that the claims fail to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, as they do not delineate the claimed subject matter with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 75, 149, and 169 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

(a) Claims 75 and 169 are drawn to the method of claim 69 and 126, respectively, wherein the antibodies or antigen binding portions thereof are administered rectally.

Claims 75 and 169 are not original claims; claim 75 was added by the amendment filed January 25, 2002, whereas claim 169 was added by the amendment filed July 7, 2003. At page 10 of that amendment filed January 25, 2002, Applicant has asserted that support for the claim is found in the specification, as filed, in the originally filed claims, as well as in the disclosure, e.g., at page 29, lines 11-29; page 13, line 11, to page 14, line 10; page 19, line 37, to page 20, line 11; page 15, lines 18-19; page 16, line 16, to page 17, line 4; page 25, lines 16-35; page 35, Table 3; page 19, lines 20-36 and Table 1; page 11, lines 21-33; page 37, line 24, to page 39, line 14; page 18, line 33, to page 19, line 7; page 40, line 14, to page 45, line 14; page 26, line 1, to page 29, line 10; page 21, lines 19-30; and page 6, lines 5-22. Then, at page 17 of that amendment filed July 7, 2003, Applicant has asserted that support for claim 169 is found throughout the specification, as filed, but does not point to any particular disclosures.

Contrary to Applicant's assertions, none of originally filed claims or any of the particular disclosures to which Applicant has referred appears to describe administering an antibody or antigen binding portion thereof *rectally*.

Originally filed claim 6 (now canceled) was drawn to a method for ablating or killing normal, benign hyperplastic, and cancerous prostate epithelial cells, wherein the antibody is administered orally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation, by intracavitory or intravesical instillation, intraocularly, intraarterially, intralesionally, or by application to mucous membranes. However, none of the originally filed claims describe administering the antibody or fragments thereof rectally.

Similarly, the originally filed disclosure describes, for example, "antisera prepared from a prostatic fluid antigen obtained by *rectal* massage from patients with prostatic disease" (page 4, lines 4-9) (italics added for emphasis) and "administering a short range radiolabeled antibody to the mammal and then *detecting the label rectally*, such as with a transrectal detector probe" (page 15, lines 17-24) (italics added for emphasis), but does not describe administering the antibody or fragments thereof rectally.

Consequently, the addition of claims 75 and 169, directed to the methods of claims 69 and 126, respectively, wherein the antibodies or antigen binding portions thereof are administered rectally, appears to have introduced new matter, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

This issue might be remedied if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary support for the language of the present claims.

(b) Claim 149 is directed to a genus of radiation-emitting compounds, which are "beta- and gamma-emitters".

Claim 149 is not an original claim; the claim was added by the amendment filed October 28, 2002. At page 15 of that amendment Applicant has asserted that support for the claim is found throughout the specification, as filed, but does not point to any particular disclosures.

Contrary to Applicant's assertions, none of originally filed claims or any of the particular disclosures to which Applicant has referred appears to describe administering an antibody or antigen binding portion thereof comprising a cytotoxic drug that is a beta-*and* gamma-radiation emitting compound.

Contrary to Applicant's assertion, it does not appear the specification, including the claims, as originally filed, provides the necessary support for the language of claims drawn to kits for detecting any of a genus of different types of cancer, with the notable exception of a kit for detecting prostate cancer.

Claim 149 finds inadequate support in the original claims, as they merely describe biological agents (e.g., antibodies), which are coupled to "radioactive labels" (e.g., claim 39) or "compounds emitting radiation" (e.g., claim 52).

Similarly, while at page 26, lines 18-25, for example, the specification describes conjugating or coupling the antibodies or antigen binding fragments to intracellularly acting cytotoxic drugs, such as short-range radiation emitters, including, for example, short-range, high-energy alpha-emitters, and at page 28, lines 17-28, it describes coupling the antibodies or fragments to coupled to high energy radiation emitters, such as ^{131}I (which incidentally is described as a "gamma-emitter") or other suitable radioisotopes including ^{212}Bi, ^{213}Bi, and ^{211}At, which are described as "alpha-emitters", and ^{186}Re and ^{90}Y, which are described as "beta-emitters", the specification fails to expressly describe any radioactive isotopes or compounds as emitting both beta- and gamma-emissions.

Notably, some of the isotopes that are particularly described are in fact beta/gamma emitters (e.g., ^{131}I; ^{90}Y; ^{111}In); nevertheless, none of those isotopes are described in the specification as emitting both beta and gamma radiation. In addition, although the specification describes some isotopes, which are beta/gamma emitters, it fails to describe the genus, as a whole, and moreover it fails to describe each and every member of the genus, as, for example, it fails to describe the beta/gamma emitters: ^{67}Cu, ^{153}Sm, and ^{165}Dy. Given that each isotope of a given element, which emits both beta and gamma radiation, is well recognized as distinct from the others because of differences, for example, in their molecular mass, or the subatomic composition of their nuclei, it is submitted that the few particularly described isotopes, which are beta/gamma emitters, should not be construed as a provision of adequate written support for claims directed to the genus. Again, although the specification describes a few isotopes, which are beta/gamma emitters, it does not describe those isotopes as members of radiation-emitting compounds, which are "beta- and gamma-emitters", and otherwise describes one or more of the genus as emitting only one or the other type of radiation, and not both.

Consequently, the addition of claim 149 appears to have introduced new matter, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

This issue might be remedied if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary support for the language of the present claims.

13. Claims 69-80, 124-127, 129, 130, 136-173, 186, and 190 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for treating prostate cancer in a subject, said method comprising administering to the subject an antibody or an antigen binding portion thereof that binds prostate specific membrane antigen (PSMA), wherein said antibody or antigen binding portion thereof is conjugated to a therapeutically effective cytotoxic agent, and wherein said first antibody or antigen binding portion thereof binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, **or while being enabling for using** any other method for treating prostate cancer in a subject, *as taught by the prior art*, which falls within the scope of the present claims, **does not reasonably provide enablement for using** a method for treating prostate cancer in a subject, said method comprising administering to the subject any antibody or an antigen binding portion thereof that competes for binding to PSMA with a J591, a J533, a E99, or a J415 monoclonal antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

> Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

(a) *The specification would not reasonably enable the skilled artisan to make the antibodies or antigen binding portions thereof to which the claims are directed without undue and/or unreasonable experimentation.*

The claims are directed to a genus of antibodies or antigen-binding fragments thereof, which do not necessarily bind PSMA, or more particularly do not necessarily bind to the same epitope as any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109. Rather, because as evidenced by George et al. (cited *supra*), for example, an antibody need not bind the same epitope of an antigen to "compete" for binding to that antigen with another antibody, the claims should broadly, but reasonably be interpreted to encompass any antibody, not necessarily an antibody

that binds to the same epitope as any of monoclonal antibodies J591, J533, E99, and J415, and perhaps not necessarily an antibody that binds to PSMA.

The claimed antibodies or antigen binding fragments thereof, which compete for binding to PSMA with any of a plurality of "E99" monoclonal antibodies, any of a plurality of "J415" monoclonal antibodies, any of a plurality of "J533" monoclonal antibodies, or any of a plurality of "J591" monoclonal antibodies, include but are not limited to antibodies or antigen-binding fragments that bind to the same or a different epitope as a member of any of the recited pluralities of monoclonal antibodies; see, e.g., paragraph [0104] of the published application. As explained above, the specification describes monoclonal antibodies J591, J533, and E99 as each capable of interfering with binding of the others to PSMA but incapable of competing for binding to PSMA with monoclonal antibodies J415 and 7E11/CYT356, and vice versa. Because each of monoclonal antibodies J591, J533, and E99 interferes with the others, the specification teaches each binds to the same epitope of PSMA; and because none of monoclonal antibodies J591, J533, and E99 interfere with the binding of monoclonal antibodies J415 and 7E11/CYT356, and vice versa, the specification teaches the latter antibodies bind different epitopes.

Furthermore, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what conditions. As evidenced by George et al. (cited *supra*), for example, at a high enough concentration, or under certain conditions, *any* antibody, but perhaps especially another antibody that binds the same antigen, or more particularly the same epitope recognized by another antibody or an overlapping epitope of the antigen, is expected to "compete" for binding to the antigen with the other antibody.

Nonetheless, regardless of how, and under which conditions, the determination that an antibody or antigen-binding fragment binds to the same or a different epitope, as compared to any member of the recited pluralities of monoclonal antibodies, is ultimately made, it is necessary to have access to those members to make the claimed invention.

Although the specification describes the deposit of hybridomas in accordance with the Budapest Treaty, which produce monoclonal antibodies J591, J533, E99, and J415 (ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively), the specification does not teach one to make these antibodies by, for example, disclosing the entirety of their amino acid sequences or the polynucleotide sequences encoding their amino acid sequences. Notably, the specification teaches only the variable regions of the light and heavy chains of "J591" monoclonal antibodies (Example 12, page 40, line 11, through page 45, line 8), but such a disclosure would not be sufficient to enable the skilled artisan to reproduce the intact monoclonal antibody to which the claims are directed. Furthermore, it is unclear if a cell line (e.g., a hybridoma) that produces an antibody having the exact structural and chemical identity as any of J591, J533, E99, or J415 is known and publicly available, or can be reproducibly isolated without undue experimentation. Without access to a hybridoma or recombinant cell line producing the monoclonal antibodies to which the claims are directed, it would not be possible to make and/or use the claimed invention, because it would not be possible to make the antibody, and then use the antibody to determine if the claimed antibody or antigen-binding fragment thereof "competes" for binding to PSMA with that antibody.

Furthermore, as explained in the rejections above, the claims are not necessarily limited to the antibodies or antigen-binding fragments that "compete" for binding to PSMA with an antibody produced by any of the deposited hybridomas; instead, the claims are more broadly directed to antibodies that compete for binding to PSMA with any of a *plurality* of "E99" monoclonal antibodies, any of a *plurality* of "J415" monoclonal antibodies, any of a *plurality* of "J533" monoclonal antibodies, or any of a *plurality* of "J591" monoclonal antibodies. However, it cannot be ascertained what "monoclonal antibodies" constitute each of the recited pluralities of monoclonal antibodies, as the specification fails to describe the particularly identifying structural and functional features of these pluralities; and one cannot make, what has not been described. If one cannot make the "monoclonal antibodies" to which the claims are directed, one cannot identify or select the claimed antibodies or antigen binding fragments thereof by

determining whether or not candidate antibodies or antigen binding fragments thereof "compete" for binding to PSMA with those "monoclonal antibodies".

If the deposit requirements *were* satisfied, the disclosure would only be sufficient to make the monoclonal antibodies J591, J533, E99, and J415, which are produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively.

However, the referrals to deposits in the specification at, for example, page 30, lines 15-27, are insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01 (p)(c) are met. Although these deposits are described as having been made under the provisions of the Budapest Treaty (page 30, lines 15-21), it does not appear Applicant has provided the necessary assurance that that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

Therefore, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Although the prior art enables one to make and use many antibodies, which under certain conditions, could demonstrably "compete" for binding to PSMA with any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, Applicant is reminded that to satisfy the enablement requirement, reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification. Furthermore, although a specification need not, and preferably

omits teachings well known in the prior art, in deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997). Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify antibodies and antigen-binding fragments thereof, which under certain, albeit unspecified assay conditions "compete" for binding to PSMA with any member of the recited pluralities of monoclonal antibodies; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

(b) *The specification would not reasonably enable the skilled artisan to use the antibodies or antigen binding portions thereof to which the claims are directed to practice the claimed invention, so as to achieve the claimed objective, without undue and/or unreasonable experimentation.*

The claims are drawn to a method for treating prostate cancer in a subject, said method comprising administering to the subject an antibody or antigen-binding portion thereof, which competes for binding for binding to PSMA with an E99, a J415, a J533, and a J591 monoclonal antibody.

Inasmuch as the claims are directed to methods for treating prostate cancer, the antibody or antigen binding portion thereof to which the claims are directed *must be therapeutically effective*, otherwise the claimed invention cannot be practiced in a manner that achieves the claimed objective.

While the specification does not expressly define the outcome (or a measured endpoint that is representative thereof) of an effective treatment necessarily achieved by the claimed invention, at page 9, lines 28-35, it is noted the specification describes

the invention as "a method of ablating or killing normal, benign hyperplastic, and cancerous prostate epithelial cells". Accordingly, it is apparent the outcome of an effective treatment may comprise, for example, the killing of cancerous prostate cells. Additionally, as the specification describes the biological agent, which is administered to the subject upon practicing the claimed invention, as either used alone or is bound to a substance effective to kill prostate cancer cells upon its binding to the cells (page 9, lines 33-35), it is apparent that the antibody or antigen binding portion thereof must be therapeutically effective *alone* to kill prostate cancer cells (i.e., in the absence of an attached therapeutic moiety), or otherwise therapeutically effective when bound to a therapeutic moiety.

Notably, the prior art teaches effective treatment of prostate cancer using antibodies that bind the extracellular domain of PSMA, albeit not necessarily antibodies that compete for binding to PSMA with an E99, a J415, a J533, and a J591 monoclonal antibody, *where the antibody is conjugated or covalently linked to a cytotoxic substance*, such as a therapeutic drug or radioisotope.

Such is the case with claims 124-127, 136-138 (in part), 139-152, 154 (in part), 155, 156-163 (in part), 164-173, 186, and 190 (in part), which are directed to members of the genus of antibodies or antigen-binding portions thereof, which comprise a cytotoxic drug (e.g., a therapeutic drug or a compound emitting radiation).

Claims 157 and 158, on the other hand, are directed, at least in part, to members of the genus of antibodies or antigen binding portions thereof, which, although not necessarily conjugated to cytotoxic drug, are nonetheless effective to initiate complement-mediated cellular cytotoxicity (CMCC) or antibody-dependent cellular cytotoxicity (ADCC) against the prostate cancer cells expressing PSMA to which they bind and are therefore therapeutically effective to kill prostate cancer cells by one or the other mechanism.

Otherwise, the claims encompass methods for treating prostate cancer in a subject, which comprise administering to the subject a *naked* antibody (i.e., an antibody that is not conjugated to a cytotoxic agent or prodrug) that competes for binding to

PSMA with an E99, a J415, a J533, and a J591 monoclonal antibody, so as to be therapeutically effective upon its administration to a subject afflicted by prostate cancer.

As will be shown, the prior art teaches that the skilled artisan cannot predict whether a naked antibody or antigen binding portion thereof, which is not conjugated to a cytotoxic moiety, is effective to kill the cells to which it binds, unless it is known that the antibody mediates ADCC or CMCC against those cells.

The specification fails to remedy the deficiency of the prior art to enable the skilled artisan to practice the claimed invention without undue and/or unreasonable experimentation, as it does not particularly describe any one antibody or antigen binding portion thereof that competes for binding to PSMA with an E99, a J415, a J533, and a J591 monoclonal antibody that is not conjugated to a therapeutically effective cytotoxic drug, and does not mediate either ADCC or CMCC, which is used to practice the claimed invention.

Moreover, there is factual evidence that *naked* antibodies that bind the extracellular domain of PSMA, as expressed by prostate cancer cells, which are not conjugated to a cytotoxic agent, have no antitumor activity. For example, Henry et al. (*Cancer Res.* 2004 Nov 1; **64**: 7995-8001) teaches an anti-PSMA immunoconjugate comprising the drug maytansinoid 1 (DM1) is effective to suppress the growth of prostate cancer in a subject, whereas the unconjugated antibody had no effect upon the growth of the cancer cells; see entire document (e.g., the abstract; and page 7998, Figure 3A). In fact, Henry et al. reports the effect of the *naked* antibody upon the growth of the tumor cells in the subject was not significantly different from the effect of the vehicle control (i.e., the buffer, PBS, which was used as a carrier); see, e.g., page 7997, column 1.

While perhaps the antibody described by Henry et al. (cited supra) does not bind to the same epitope of the extracellular domain of PSMA as any of the monoclonal antibodies E99, J415, J533, and J591, which are described in the instant application, and may not be effective to substantially compete for binding to PSMA with these antibodies, there is no factual evidence of record that suggests the lack of effect by the naked antibody of Henry et al. is explained by it binding to a different epitope.

Nonetheless, McDevitt et al. (*Cancer Res.* 2000 Nov 1; **60**: 6095-6100) notably reports an alpha-particle emitting radioimmunoconjugate comprising monoclonal antibody J591 effectively stopped the growth of LNCaP prostate cancer cells *in vitro*, but the unlabeled monoclonal antibody produced no substantial effect; see entire document (e.g., the abstract; and page 6098, Figure 4).

So even were an antibody to bind to the same epitope as any of monoclonal antibodies E99, J415, J533, and J591, the prior art shows the skilled artisan cannot predict whether that antibody, conjugated or not to a cytotoxic agent, is used effectively to kill the cells to which it binds. Consequently, the disclosure would not have reasonably enabled the skilled artisan to practice the claimed invention, as of the filing date sought by Applicant, without undue and/or unreasonable experimentation, as the therapeutic effectiveness of the antibody or antigen binding portion thereof, if not conjugated to a cytotoxic drug or prodrug, or not known to mediate ADCC or CCMC, must be determined empirically.

Notably, Morris et al. (*Clin. Cancer Res.* 2005 Oct 15; **11** (2): 7454-7461) discloses, prior to October 2005, the *in vivo* activity of unlabeled, naked humanized antibody J591, and particularly its ability to activate therapeutically effective ADCC in treated subjects, had not been explored; see entire document (e.g., the abstract). Although Morris et al. reports, "increasing doses of antibody are associated with higher rates of patients with ADCC reactivity [...] and higher median percent LNCaP cell lysis" (page 7458, column 2), Morris et al. also reports only one of 14 patients had any measurable objective response, as determined by measurement of the surrogate endpoint, namely a PSA decline[2], whereas 11 patients progressed, one had a marginal response, and one showed stable disease (page 7459, column 1). Moreover, Morris et al. teaches the antibody is ineffective to mediate CMCC, as it does not bind complement

[2] The patients were treated with radiolabeled, or a combinantion of radiolabeled and unlabeled deimmunized monoclonal antibody J591 (page 7455, paragraph bridging columns); and Morris et al. does not indicate whether the growth inhibitory effects of the treatment were mediated by the resultant irradiation of the targeted prostate cancer cells, by ADCC, or both.

and therefore not surprisingly induced no significant change in C3 and C4 levels in the treated subjects (page 7458, column 2).

While there is an assertion in the specification that any of monoclonal antibodies E99, J415, J533, and J591 may be effective to mediate ADCC or CCMC, it discloses no data or scientifically based reasoning to support the assertion[3]. Accordingly, in view of Morris et al. (cited *supra*), it would seem as of the filing date sought by Applicant the claimed invention could not have been practiced, even using the particularly described monoclonal antibody J591, without undue and/or unreasonable experimentation, as it would have first been necessary to empirically determine whether the antibody or portion thereof effectively mediates ADCC or CMCC[4], and then whether it is used effectively to treat prostate cancer in a subject.

The prior art teaches the skilled artisan cannot predict the effect of an antibody upon the growth of cancer cells, since it is well understood that antibodies binding the same antigen, or even the same epitope of an antigen, may have strikingly different

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[3] The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). The prior art shows the skilled artisan cannot predict whether any given antibody or portion thereof, which binds to PSMA, is capable of mediating ADCC or CMCC.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that describes with particularity any one member of the genus of antibodies or portions thereof that bind PSMA-expressing prostate cancer cells to mediate ADCC or CMCC against those cells. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

"Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the antibodies to which the claims are directed, it is impossible to use the claimed invention.

[4] Kim et al. (*Int. J. Cancer.* 2002; **102**: 428-434) teaches the skilled artisan cannot predict whether an antibody or portion thereof is capable of mediating ADCC, since it ability to do so depends upon both the isotype of the antibody and the epitope of the antigen to which it binds; see entire document (e.g., the abstract).

In addition, Kinoshita et al. (*Prost. Cancer Prost. Dis.* 2005; **8**: 359-363) teaches the need to identify the epitopes of PSMA to which antibodies capable of mediating ADCC bind; see entire document (e.g., page 359, column 2).

effects. For example, Stancoviski et al. *(Proceedings of the National Academy of Science USA.* 1991; **88**: 8691-8695) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually *accelerated* their growth (page 8693, column 1). Xu et al. (*Int. J. Cancer.* 1993; **53**: 401-408) has characterized similarly differential effects of another panel of antibodies that bind the same antigen, albeit different epitopes; see entire document (e.g., the abstract). By way of explanation, Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662) teaches that it is well known that different biological effects are associated with epitope specificity of the antibodies; see entire document, particularly page 4656, column 2. In addition, De Santes et al. (*Cancer Res.* 1992 Apr 1; **52**: 1916-1923) teaches administering radiolabeled anti-ErbB2 (Her-2/*neu*) monoclonal antibody 4D5 to a subject caused a marked inhibition of tumor growth in the subject; however, the unlabeled, naked antibody had no effect on tumor progression; see entire document (e.g., the abstract; page 1921, Figure 7). Again, as indicated above, unless the antibody or antigen binding portion thereof is conjugated to a cytotoxic drug, the prior art teaches it cannot be determined *a priori* whether an antibody is capable of inhibiting the growth of cancer cells, or more particularly, whether it is used effectively to treat prostate cancer. Moreover, the prior art teaches the effectiveness of an antibody is necessarily determined empirically, and consequently, as of the filing date sought by Applicant, the skilled artisan could not have used the claimed invention without undue and/or unreasonable experimentation.

It follows from the above discussion of the related prior art that the mere generalized description of antibodies, as binding a well-characterized tumor-associated antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to adequately describe the antibodies to which the claims are directed, namely antibodies that have an inhibitory and therapeutic effect, because the skilled artisan could not distinguish those antibodies that bind an antigen on tumor cells and inhibit the

growth of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells) without undue and/or unreasonable experimentation.

In further support of this position, Boyer et al. (*Int. J. Cancer.* 1999; **82**: 525-531) teaches different epitopes of a tumor-associated antigen (i.e., Her-2) can serve as distinct targets for immunotoxins; see entire document (e.g., the abstract). Boyer et al. teaches a panel of antibodies conjugated to a cytotoxic moiety, which bind to discrete epitopes, produced markedly different cytotoxic effects that did not correlate with the isotype of the antibody, its binding affinity, the relative position of its epitope, or its internalization by the targeted cells; see, e.g., the abstract. Similar epitopic-dependency has been described by Press et al. (*J. Immunol.* 1988 Dec 15; **141** (12): 4410-4417); ricin A-chain comprising immunotoxins directed against different epitopes of an antigen differ markedly in their ability to kill the targeted cells (see entire document, e.g., the abstract).

Indeed, Riemer et al. (*Mol. Immunol.* 2005; 42: 1121-1124) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine the diverse biological effects; see entire document, particularly page 1123, column 1.

The epitope of PSMA to which monoclonal antibodies E99, J415, J533, and J591 bind has not been characterized, so it is not plausible that the skilled artisan can select an antibody that binds to the same epitope as any one of these antibodies without undue and/or unreasonable experimentation[5].

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[5] The term "epitope", as it is used in the art of immunology, is more generally used in a broader context to mean an "antigenic determinant", or site on the surface of an antigen molecule to which a single immunoglobulin molecule (e.g., antibody) binds; generally an antigen has several or many different antigenic determinants and reacts with antibodies of many different specificities. Stedman's Online Medical Dictionary, 27th Edition; which is available on the Internet at http://www.stedmans.com/, for example, defines the term "epitope' as "[t]he simplest form of an antigenic determinant, on a complex antigenic molecule, which can combine with antibody or T cell receptor".

Again, Greenspan et al. (cited *supra*), for example, teaches that defining epitopes is not as easy as it seems; and given this fact, it follows the epitope to which any given ligand binds can only be identified empirically.

Were the antibody to which the claims are directed to bind an overlapping, as opposed to the same epitope, the prior art teaches the skilled artisan cannot predict whether the antibody, even when conjugated to a cytotoxic moiety, is used effectively to treat prostate cancer. For example, Pettersen et al. (*J. Immunol.* 1999 Jun 15; **162** (12): 7031-7040) teaches anti-hIAP (CD47) monoclonal antibodies Ad22 and 1F7, which induce apoptosis of Jurkat T cells and peripheral blood mononuclear cells (PBMC) expressing the antigen to which these antibodies bind; but Pettersen et al. also teaches other antibodies, namely monoclonal antibodies 2D3 and B6H12 that commonly bind to hIAP/CD47, which *do not induce apoptosis* of the cells to which it binds; see entire document (e.g., the abstract; and page 7033, column 1). As might be expected, given the recognized epitope-dependency of the various effects caused by different antibodies binding the same antigen, Pettersen et al. teaches monoclonal antibody 2D3 and Ad22 bind discrete epitopes; but curiously Pettersen et al. teaches monoclonal antibody B6H12, despite its apparent inability to induce apoptosis, binds an epitope that overlaps the epitopes to which monoclonal antibodies Ad22 and 1F7 (see, e.g., page 7032, column 2). Similarly, Bernard et al. (*Human Immunol.* 1986; **17**: 388-405) describes differential effects by antibodies binding "competing" antigenic sites or epitopes. Thus, the prior art suggests that a description of a genus of antibodies as competing for binding of another antibody known to cause a desired effect may not be sufficient to describe the genus of antibodies having that same effect; and as such, it is submitted the claimed invention could not be practiced, as of the filing date sought by Applicant, without undue and/or unreasonable experimentation, as it would be necessary to empirically determine whether or not an antibody or portion thereof is used effectively to treat prostate cancer.

Thus, as explained above, even using a competition binding assay, such as that described in Example 10 of the specification, the skilled artisan cannot recognize or distinguish an antibody that binds the same epitope as another antibody because antibodies that compete with one another for binding to the same antigen do not necessarily bind the same epitope; rather, an antibody may bind a spatially overlapping epitope and thereby sterically hinder binding of the other ligand to its epitope, or as evidenced by George et al. (discussed in further detail below), an antibody may bind an epitope that is distant from, and spatially non-overlapping with the epitope of an antigen recognized by the other antibody, and still interfere with binding of the latter to the antigen.

Now, having made that point, despite any assertion otherwise, it is aptly noted that claims are not necessarily directed to antibodies or antigen binding fragments thereof that bind to the same epitope of PSMA as any of monoclonal antibodies E99, J415, J533, and J591.

The specification alleges that an antibody that competes for binding to PSMA with an E99, a J415, a J533, and a J591 monoclonal antibody necessarily binds the same antigenic determinant or epitope; see, e.g., page 37, line 24, through page 39, line 16. This is not necessarily true, as will be explained; and it is aptly noted that the term "competes" is not expressly defined in the specification, so it is not immediately determinable, given the instant disclosure, what functional attribute characterizes the antibody or antigen binding fragment thereof, which is used effectively in practicing the claimed invention; moreover, it is further noted, as discussed in greater detail below, the requisite degree to which the antibody "competes" for binding to PSMA with any one of the recited monoclonal antibodies, nor the methodology used to make such a determination, and the conditions under which that determination are made, are ascertainable from the disclosure. As such, it is submitted the amount of guidance, direction, and exemplification set forth by the disclosure is not reasonable commensurate in scope with the breadth of the claims, would not permit the skilled artisan to immediately identify antibodies that are suitable, and would not therefore reasonably enable the practice of the claimed invention without undue and/or unreasonable experimentation.

As noted above, the term "competition" is defined, for example, by Stedman's Online Medical Dictionary, 27th Edition as meaning: "The process by which the activity or presence of one substance interferes with, or suppresses, the activity of another substance with similar affinities" (Copyright © 2006 Lippincott Williams & Wilkins). Given this definition, the claims are directed to antibodies or antigen-binding fragments thereof that interfere with, or suppress binding of one of the selected monoclonal antibodies to PSMA, as perhaps determined using the exemplified binding assay.

Again, this interpretation is not inconsistent with the specification, which at paragraph [0106], for example, discloses: "The results indicated that J591, J533, and

E99 each **interfere, compete, or block** binding of one another but do not block binding of J415 and vice versa" (emboldened for emphasis).

Thus, while one may know how to determine whether an antibody "competes" with one of the selected monoclonal antibodies, it is apparent that the degree to which an antibody competes with another antibody is a relative or subjective expression, and the requisite degree to which the claimed antibody competes with any of the selected monoclonal antibodies cannot be ascertained from the disclosure.

Contrary to the assertion in the specification that such a binding assay determines whether two antibodies bind to the same antigenic determinant (i.e., epitope), competing antibodies do not necessarily bind the same epitopes. For example, "competing" antibodies may bind spatially overlapping but discrete epitopes. Simply because two antibodies cannot simultaneously occupy the same space, such an antibody, once bound to the antigen, sterically hinders or blocks binding of another such antibody. As another example, a "competing" antibody might not necessarily bind to the same epitope of an antigen as another antibody, if one of the antibodies induces conformational shifts in the three-dimensional structure of the antigen upon binding, which prevents binding of the other antibody to the antigen because the epitope to which it would otherwise bind is unrecognizable as a consequence of the structural change.

In addition, it is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

As explained above, George et al. (cited *supra*), for example, describes different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of competing with one another for binding to the antigen; see entire document

(e.g., page 903, paragraph bridging columns 1 and 2). Furthermore, as also explained above, George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification. Again, although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

It cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the selected antibody and PSMA. If the claimed antibody merely inhibits binding of the selected antibody to PSMA, it cannot be determined to what requisite extent the claimed antibody must "compete" for binding to PSMA with the selected antibody.

In addition, it is aptly noted the claims are not necessarily limited to the antibodies produced by any of the deposited hybridomas, as they are instead more broadly directed to antibodies that compete for binding to PSMA with any of a *plurality* of "E99" monoclonal antibodies, any of a *plurality* of "J415" monoclonal antibodies, any of a *plurality* of "J533" monoclonal antibodies, or any of a *plurality* of "J591" monoclonal antibodies. Pointedly, different members of these different pluralities of antibodies do not necessarily bind PSMA with the same affinity or avidity as any of the monoclonal antibodies produced by any of the deposited hybridomas. For example, a humanized "J591" antibody may have a substantially different binding affinity than the murine monoclonal antibody produced the deposited hybridoma. Presuming the concentration of the antibody is not altered, depending upon the affinity and avidity that characterizes any given antibody's ability to bind an antigen, the antibody is expected to more or less effectively "compete" with another antibody that binds the same antigen. Furthermore, different members of these different pluralities of antibodies are not necessarily therapeutically equivalent, since, for example, the humanized monoclonal antibody might be capable of mediating ADCC, whereas the murine antibody is not. For example, Lewis et al. (*Cancer Immunol. Immunther.* 1993; **37**: 255-263) teaches murine

monoclonal antibody 4D5 lacks effector function and does not mediate ADCC or CMCC, but a humanized version of the same antibody does; see entire document (e.g., page 260, column 2, through page 261, column 1).

Although the prior art enables one to make and use many antibodies, which under certain conditions, could demonstrably "compete" for binding to PSMA with any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, and while the skilled artisan could potentially screen such "competing" antibodies to identify those that are therapeutically effective to treat prostate cancer, Applicant is again reminded that to satisfy the enablement requirement, reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification. Furthermore, although a specification need not, and preferably omits teachings well known in the prior art, in deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify antibodies and antigen-binding fragments thereof, which under certain, albeit unspecified assay conditions "compete" for binding to PSMA with any member of the recited pluralities of monoclonal antibodies; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

With particular regard to claim 156, which is directed to the method of claim 69, 125, 126, or 127, wherein the antibody or antigen binding portion thereof is effective to initiate an endogenous host immune function, most murine monoclonal antibodies, which are administered to humans, are effective to initiate an immune response against the antibodies. However, this property of the murine antibodies is generally recognized as a limitation to the effective treatment of humans, as the resultant immune response preclude repeated administrations that will likely cause undesired and potentially harmful side-effects (e.g., immune hypersensitivity, and perhaps anaphylactic shock).

Accordingly, it is submitted that the disclosure does not reasonably enable the use of the claimed invention, as it would not be practiced effectively using antibodies capable of initiating any and all types of endogenous host immune functions, but perhaps only such immune responses that are therapeutically efficacious against prostate cancer cells, such as ADCC or CMCC.

Finally, with regard to claim 190, which is directed to method according to claim 69, 124, 125, 126, or 127, which is effective to prevent or delay the progression of prostate cancer in the subject, the amount of guidance, direction and exemplification would not reasonably enable the skilled artisan to use the claimed invention without undue and/or unreasonable experimentation. If the antibody or antigen binding portion thereof were administered to a subject prior to the onset of the disease, so as to prevent its occurrence, it is submitted the specification fails to provide the guidance and direction necessary to select patients in whom the invention is used effectively, and moreover, as PSMA is expressed by normal prostatic epithelial cells, as well as other normal tissue, it would seem likely that the cost of such treatment would outweigh the benefit, as the treatment would undesirably affect the growth and/or survival of normal cells. Furthermore, there is no factual evidence of record that supports the assertion that the disease is preventable, regardless of whether or not the patient is treated using the claimed invention. Similarly, there is no factual evidence of record that supports the assertion that the claimed method is effective to prevent the progression of the disease, as Morris et al. (cited *supra*), for example, teaches to the contrary monoclonal antibody J591 was not effective to prevent disease progression (page 7459, column 1).

Accordingly, there is a preponderance of factual evidence, now of record, that contrary to the assertions set forth in the specification, the skilled artisan could not practice the claimed invention to effectively treat prostate cancer in a subject without undue and/or unreasonable experimentation because the disclosure would not reasonably enable one to make, identify, and/or select an antibody that is used effectively to do so.

Therefore, in conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal

Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 69-71, 77-80, 125, 126, 129, 130, 136-140, 144, 150, 152-154, 156-161, 164, 165, 171-173, 186, and 190 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,962,981 B1, as evidenced by Liu et al. (*Cancer Res.* 1998 Sep 15; **58**: 4055-4060) (of record; cited by Applicant) and George et al. (*Circulation*. 1998; **97**: 900-906).

U.S. Patent No. 6,962,981 B1 (Murphy et al.) teaches monoclonal antibodies and antigen binding fragments thereof that bind specifically to the extracellular domain of PSMA and methods of using the antibodies for prostate cancer diagnosis and treatment; see entire document (e.g., the abstract; column 3, lines 10-16; Figure 20; column 27, Table 2). Murphy et al. teaches antibodies are used for tumor localization for detection and monitoring, as well as for therapy of primary prostate carcinoma and metastases, such as bone metastases of prostate cancer; see, e.g., column 14, lines 5-8; and column 9, lines 50-52. Murphy et al. teaches hybridomas producing the

disclosed monoclonal antibodies; see, e.g., columns 29 and 30. Murphy et al. teaches the fragments of the disclosed monoclonal antibodies are Fab fragments, F(ab')2) fragments, and Fv fragments; see, e.g., column 14, lines 8-17. Murphy et al. teaches the disclosed monoclonal antibodies or antigen binding fragments thereof are conjugated (bound) to a cytotoxic drug, namely radioisotopes, chemotherapeutic drugs, and toxins; see, e.g., column 14, lines 37-52. Murphy et al. teaches the antibodies or antigen binding fragments thereof are conjugated to beta-emitters (i.e., positron emitting isotopes); see, e.g., column 14, lines 25-36. Murphy et al. teaches the antibodies or antigen binding fragments thereof are conjugated to streptavidin[6] and other biological proteins, which are used as therapeutic agents; see, e.g., column 15, lines 10-30. Murphy et al. teaches the antibodies or antigen binding fragments thereof are labeled with any of a variety of "reporter" substances, including, for example, radioactive isotopes and fluorogenic compounds; see, e.g., column 14, lines 26-36. Murphy et al. teaches compositions comprising the antibodies or antigen binding fragments thereof, which are suitably used in a variety of applications, including immunohistological and immunocytochemical applications, and diagnostic and therapeutic applications; see, e.g., column 11, line 26, through column 15, line 30. For example, Murphy et al. teaches an effective amount of the antibody is administered to a patient afflicted by prostate cancer and antibody kills and/or inhibits proliferation of the malignant cells after localization at sites of primary or metastatic tumors bearing PSMA; see, e.g., column 14, line 37, through column 15, line 5. Furthermore, Murphy et al. teaches the antibody mediates tumor destruction by complement fixation (CMCC) or antibody-dependent cellular cytotoxicity (ADCC); see, e.g., column 14, lines 37-44. Accordingly, such compositions, particularly those used in therapeutic compositions, are necessarily further comprised of pharmaceutically acceptable carriers, excipients, and/or stabilizers. Murphy et al. teaches kits for use, for example, in diagnosing prostate cancer, which comprise such compositions comprising the disclosed antibodies or antigen binding

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[6] Notably, streptavidin is a biological protein of bacterial origin. Murphy et al. teaches antibodies conjugated to streptavidin and bound to a biotinylated cytotoxin are used therapeutically; see, e.g., column 15, lines 26-30.

fragments thereof; see, e.g., column 15, lines 31-43. Murphy et al. teaches the antibody is used in combination with other therapeutic modalities, such as a chemotherapeutic drug; see, e.g., column 14, lines 45-48. Murphy et al. teaches the antibodies or antigen binding portions thereof bind live cells; see, e.g., column 28, lines 38-43.

Although Murphy et al. does not expressly teach any of the disclosed antibodies or antigen binding fragments thereof "compete" for binding to PSMA with monoclonal antibodies J591, J415, J533, and /or E99, *because the disclosed antibodies bind the extracellular domain of PSMA* (see, e.g., Figure 20), there is a reasonable presumption that the antibodies bind the same or an overlapping epitope of PSMA as those recognized by one or more of monoclonal antibodies J591, J415, J533, and E99.

Moreover, as evidenced by George et al. (cited *supra*), it is aptly noted that an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody. Thus, at a high enough concentration, or under certain conditions, *any* antibody, but perhaps especially another antibody that binds the same antigen, or more particularly the same epitope recognized by another antibody or an overlapping epitope of the antigen, is expected to "compete" for binding to the antigen with the other antibody. As thoroughly explained above in the rejections of claims under 35 U.S.C. § 112, first and second paragraphs, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what conditions. Therefore, absent a showing of any difference, the antibodies and antigen binding fragments disclosed by Murphy et al. are deemed the same as the claimed antibodies and antigen binding fragments thereof.

Notably, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the antibodies and antigen binding fragments thereof. Moreover, the Office does not have assess to the monoclonal antibodies J591, J415, J533, and E99; and without these antibodies, it is not possible to empirically determine whether or not any of the antibodies disclosed by the prior art, particularly those which bind the

extracellular domain of PSMA, are capable of competing for binding to PSMA with one or more of those antibodies. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the antibodies and antigen binding fragments thereof are different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Furthermore, although Murphy et al. does not expressly teach any of the disclosed antibodies is internalized with PSMA, as evidenced by Liu et al., each of monoclonal antibodies J591, J415, J533, and E99 are internalized with PSMA by LNCaP cells (see entire document; e.g., page 4056, column 1). Accordingly, there is a reasonable presumption that the antibodies disclosed by Murphy et al., which bind to the extracellular domain of PSMA, are internalized with the antigen, particularly since the disclosed antibodies are deemed to "compete" for binding to PSMA with monoclonal antibodies J591, J415, J533, and /or E99.

16. Claims 69, 77-80, 125-127, 129, 130, 136, 137, 139-141, 147, 150-155, 159, 171-173, 186, and 190 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,538,866 A (of record; cited by Applicant), as evidenced by George et al. (*Circulation*. 1998; **97**: 900-906) and Liu et al. (*Cancer Res.* 1998 Sep 15; **58**: 4055-4060) (of record; cited by Applicant).

U.S. Patent No. 5,538,866 A (Israeli et al.) teaches polyclonal and monoclonal antibodies that bind specifically to PSMA, which are conjugated to a cytotoxic agent and administered to patient afflicted with prostate cancer to treat the disease; see entire document (e.g., the abstract; column 6, lines 44-47 and lines 53-5; column 13, lines 5-9; and column 23, line 3, through column 24, line 23). Israeli et al. teaches the antibody binds the extracellular domain of the antigen, so as to be capable of binding to the surface of prostate cancer cells expressing the antigen; see, e.g., column 13, lines 10-18. Israeli et al. teaches the antibody is conjugated to a cytotoxic drug, namely a radioisotope or biological toxin, such as endotoxin or ricin, which are proteins of bacterial and plant origins, respectively; see, e.g., column 13, lines 5-9; and column 23,

lines 44-52. Notably, radioisotopes are detectable labels. Israeli et al. teaches the antibody is conjugated to Indium^{111}, a gamma ray emitter; see, e.g., column 13, lines 17 and 18. Israeli et al. teaches a composition comprising the antibody and a pharmaceutically acceptable carrier, excipient, or stabilizer; see, e.g., column 13, lines 22-24. Israeli et al. teaches hybridomas producing the disclosed antibodies; see, e.g., column 12, lines 55-60.

Although Israeli et al. does not expressly teach any of the disclosed polyclonal or monoclonal antibodies or antigen binding fragments thereof "compete" for binding to PSMA with monoclonal antibodies J591, J415, J533, and /or E99, *because the disclosed antibodies bind the extracellular domain of PSMA* (see, e.g., Figure 20), there is a reasonable presumption that the antibodies bind the same or an overlapping epitope of PSMA as those recognized by one or more of monoclonal antibodies J591, J415, J533, and E99.

This is presumption is particularly reasonable, where the antibody is a polyclonal antibody, since such polyclonal antibodies are fully expected to comprise a plurality of antibodies that recognize and bind specifically to any and all antigenic determinants of the extracellular domain of PSMA, including the particular antigenic determinants (i.e., epitopes) to which one or more of monoclonal antibodies J591, J415, J533, and E99 bind.

Moreover, as evidenced by George et al. (cited *supra*), an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody. Thus, at a high enough concentration, or under certain conditions, *any* antibody, including an antibody that binds to a different epitope of an antigen than the epitope recognized by another antibody that binds the antigen is expected to "compete" for binding to the antigen with the other antibody. Neither the claims nor the disclosure delineate the conditions under which such a determination was made. Moreover, as thoroughly explained above in the rejections of claims under 35 U.S.C. § 112, first and second paragraphs, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what

conditions. Nevertheless, the antibodies disclosed by the prior art are polyclonal; polyclonal antibodies raised against PSMA bind a plurality of epitopes of PSMA, and are reasonably expected to comprise one or more species of antibody that bind to the same epitopes as monoclonal antibodies J591, J415, J533, and/or E99 and thereby "compete" for binding to PSMA with one or more of the monoclonal antibodies. In addition, because the disclosed antibodies bind the extracellular domain of PSMA, there is a reasonable presumption that the disclosed monoclonal antibodies also "compete" for binding to PSMA with one or more of the recited monoclonal antibodies, especially since, under certain conditions, any monoclonal antibody that binds to PSMA is expected to "compete" to some measurable extent for binding to PSMA with one or more of those antibodies. Therefore, absent a showing of any difference, the polyclonal or monoclonal antibodies disclosed by Israeli et al. are deemed the same as the claimed antibodies and antigen binding fragments thereof.

Again, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the antibodies and antigen binding fragments thereof. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the antibody disclosed by the prior art differs from the claimed antibody.

While Israeli et al. may not expressly teach the antibody or antigen binding portion thereof binds "live" cells, Israeli et al. discloses, for example, the antibodies are useful to detect the expression of PSMA in *living* animals (see, e.g., column 12, lines 61 and 62); but moreover it is readily understood and appreciated that the prostate cancer cells expressing PSMA to which the antibody binds, so as to ultimately kill those cells, are very much *alive*.

Furthermore, although Israeli et al. does not expressly teach any of the disclosed antibodies is internalized with PSMA, as evidenced by Liu et al., each of monoclonal antibodies J591, J415, J533, and E99 are internalized with PSMA by LNCaP cells (see entire document; e.g., page 4056, column 1). Accordingly, there is a reasonable presumption that the antibodies disclosed by Israeli et al., which bind to the extracellular

domain of PSMA, are internalized with the antigen, particularly since the disclosed antibodies are deemed to "compete" for binding to PSMA with monoclonal antibodies J591, J415, J533, and /or E99.

Accordingly, all the limitations of the rejected claims have been met[7].

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 70, 71, 160, 161, 164, and 165 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,538,866 A (of record; cited by Applicant), as evidenced by George et al. (*Circulation*. 1998; **97**: 900-906).

As evidenced by George et al., U.S. Patent No. 5,538,866 A (Israeli et al.) teaches that which is set forth in the above rejection of claims under 35 U.S.C. § 102(b).

Israeli et al., however, does not expressly teach treating metastatic prostate cancer involving the bone marrow or a lymph node metastasis; and additionally, Israeli et al. does not expressly teach using the disclosed method for treating prostate cancer in conjunction with a second therapeutic modality, or more particularly in conjunction with surgery, radiation, chemotherapy, immunotherapy, or hormone replacement.

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[7] Notably, this reference was previously applied earlier in the prosecution of this application as prior art in a rejection under 35 U.S.C. § 102(e) of then pending claims, which were directed to antibodies or antigen binding portions thereof that bind to the extracellular domain of PSMA. Applicant subsequently amended the claims, so as to be directed to antibodies or antigen binding portions thereof that bind to the epitope recognized by any one of monoclonal antibodies J591, J415, J533, and E99, arguing the prior art does not teach each and every element of the claims, as Israeli et al. does not teach or suggest antibodies that bind to the specific epitopes recited in the claims. As the present claims are not so limited, and are instead directed to any antibody or antigen binding portion thereof capable of competing for binding to PSMA with any one of a J591, a J415, a J533, and an E99 monoclonal antibody, Applicant's recorded argument in traversal of the rejection of the prior claims as being anticipated by Israeli et al. is presently immaterial.

Nonetheless, Israeli et al teaches PSMA is highly expressed in primary prostate tumors, as well as bone and lymph node metastases thereof; see, e.g., column 3, lines 3-22.

Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to treat metastatic prostate cancer involving the bone marrow or a lymph node metastasis in accordance with the invention disclosed by Israeli et al. because Israeli et al. teaches the antibody binds PSMA, which is used to treat prostate cancer, and also teaches the antigen PSMA is highly expressed in primary prostate tumors, as well as bone and lymph node metastases thereof. Furthermore, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to treat primary and/or metastatic prostate cancer in a patient using the invention disclosed by Israeli et al. in conjunction with a second therapeutic modality, or more particularly in conjunction with surgery, radiation, and/or chemotherapy, given that such treatment combinations were, and still are the standard of care. One ordinarily skilled in the art at the time of the invention would have been motivated to do so because Israeli et al. teaches, for example, that prostate cancer represents the second leading cause of death from cancer in man, and the disease may progress rapidly, metastasizing and killing the man in a relatively short period of time if is not effectually treated to alleviate its pathologic manifestation and symptoms (see, e.g., column 1, lines 16-30).

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 69, 70, 71-74, 77-80, 125-127, 129, 130, 136-141, 147, 150-155, 159, 160, 161, 164-168, 171-173, 186, and 190 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12 and 15-22 of U.S. Patent No. 6,136,311 A in view of U.S. Patent No. 5,538,866 A (of record; cited by Applicant).

Claims 12 and 15-22 of U.S. Patent No. 6,136,311 A (Bander) are directed to a method for ablating or killing cancerous cells comprising providing administering to a living mammal a monoclonal antibody or antigen binding portion thereof that binds to the extracellular domain of PSMA and is coupled to a drug effective to kill or ablate the cancerous cells. More particularly, according to claims 18 and 19, the monoclonal antibody is E99, J415, J533, or J591, or the monoclonal antibodies produced by hybridomas having the ATCC accession numbers HB-12101, HB-12109, HB-12127, or HB-12126. Notably, these antibodies bind to the same epitope(s) as monoclonal antibodies J591, J415, J533 and/or E99 and therefore "compete" for binding to PSMA with any one or more of those monoclonal antibodies. According to claim 20, the antigen binding portion of the monoclonal antibody is selected from a Fab fragment, a

F(ab')2 fragment, and a Fv fragment. According to claim 15, the antibody is internalized by the cells with PSMA upon its binding to the antigen. According to claims 21 and 22, the antibody is formulated as a composition further comprising a physiologically acceptable carrier, excipient, or stabilizer. According to claim 17, the composition comprising the antibody or antigen binding portion thereof is administered via any one of several recited routes, which are well known to the artisan of ordinary skill, including, for example, parenterally, intravenously, or by intracavitary instillation.

Although none of claims 12 and 15-22 of Bander teach or suggest the cancerous cells ablated or killed by the invention are prostate cancer cells, or more particularly metastatic prostate cancer cells, the specification defines the term "cancerous cells" as inclusive of prostate cancer cells by disclosing: "The methods of the present invention are particularly useful to kill or ablate cancerous prostate epithelial cells as well as cancerous cells other than cancerous prostate epithelial cells" (column 9, lines 17-20).

Moreover, U.S. Patent No. 5,538,866 A teaches that which is set forth in the above rejection of claims 69, 77-80, 125-127, 129, 130, 136, 137, 139-141, 147, 150-155, 159, 171-172, 186, and 190 under 35 U.S.C. 102(b) as being anticipated by the reference; and In view of those teachings, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have used the process of claims 12 and 15-22 of Bander to treat prostate cancer, or more particularly metastatic prostate cancer involving the bone marrow in accordance with any of the rejected claims.

21. Claims 69-71, 77-80, 124-127, 129, 130, 136-155, 159-161, 164, 165, 171-173, 186, and 190 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 55-59 and 172-296 of copending Application No. 10/449,379. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 55-59 and 172-296 of copending Application No. 10/449,379 are drawn to a method for treating a prostatic cancerous disorder in a subject, said method comprising administering to the subject an antibody or antigen binding portion thereof

that binds PSMA. According to claim 179, for example, the antibody or antigen binding portion thereof is associated with or coupled to at least one cytotoxic moiety, such as a compound that emits radiation or a biological protein of plant or bacterial origin; see, e.g., claim 180.

The antibodies or antigen binding portions thereof to which copending claims 55-59 and 172-296 are specifically directed are recombinant "deimmunized" versions of monoclonal antibody J591. These antibodies bind to the same epitope as monoclonal antibodies J591 and therefore "compete" for binding to PSMA with any one or more of monoclonal antibodies J591, J533, and E99.

Without further explanation, which should not be necessarily, it is aptly noted the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 69-71, 77-80, 127, 129, 130, 136, 139, 140, 151, 159-161, and 190 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-61 of copending Application No. 11/219,563. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-61 of copending Application No. 11/219,563 are drawn to a method for treating prostate cancer in a subject, said method comprising administering to the subject an antibody or antigen binding fragment thereof that binds the extracellular domain of PSMA and is coupled to a $DM1^{8}$. According to claims 2 and 3, for example, the prostate cancer is a metastatic prostate cancer involving bone marrow or lymph

node metastasis. According to claim 13, for example, the antibody or antigen binding fragment thereof is a recombinant "deimmunized" version of monoclonal antibody J591. Such antibodies bind to the same epitope as monoclonal antibodies J591 and therefore "compete" for binding to PSMA with any one or more of monoclonal antibodies J591, J533, and E99.

Without further explanation, which should not be necessarily, it is aptly noted the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

23. No claim is allowed.

24. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Liu et al. (Cancer Res. 1997 Sep 1; **57**: 3629-3634) (of record; cited by Applicant) teaches monoclonal antibodies 7E11, J591, J533, J415, and E99 should be therapeutically and diagnostically useful.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

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[8] DM1 is a derivative of ansamitocin P-3, which is maytansinoid isolated from members of the

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
November 20, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

moss family, and is therefore of plant origin.